COVID Information Commons (CIC) Research Lightning Talk

Transcript of a Presentation by Jeffrey Townsend (Yale University), June 9, 2021

Title: RAPID: Analyses of polymorphism and divergence to illuminate molecular evolution permissive of zoonoses in SARS and COVID-19

Jeffrey Townsend CIC Database Profile

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Transcript

Jeffrey Townsend:

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Thanks for tuning in for this. I'm going to talk today about the durability of immunity following affection by SARS-CoV-2, and this is a collaboration led by me with a bunch of members of my lab and some other folks who have worked on it with me or are listed here.

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So, start from the beginning, the durability of immunity upon natural infection has been called by many the greatest unknown factor of the COVID-19 epidemic. Just to give you some examples of this, on the left you see a nature video talking about the big questions six months on. The major one of which that they highlighted was what is the durability of immunity once you get infected? Secondly, on the right is a news article from STAT, seven months later what we know about COVID-19 and the pressing questions that remain, and in there, you'll find that one of the ones they highlight to the greatest degree is what is the durability of immunity of COVID-19?

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Now, most of the studies that have spoken about this topic have done longitudinal observation looking at the decline of some kind of antibody response after infection by SARS-CoV-2. The difficulty with doing that on SARS-CoV-2 and getting a result is that the decline of antibody level occurs fairly slowly, and as

you can see in this one of the first papers that came out. Essentially, there's not much decline here there's just the increase consequent to infection in these three different IgG types and then sort of a leveling off and in a few individuals there's a little bit of decline, but really on average you're not seeing the decline yet. And that's characteristic, actually, of all coronaviruses that they tend to decline- start declining around 90 days, and that's already three months in advance and a short epidemic like this there's just not enough information to figure out what the decline of antibodies is and what its correlation with immunity is.

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So that news, that in fact, you know, that in fact antibodies may decline sparked some fears that immunity to COVID-19 wanes fast. This is just a news article saying studies show coronavirus antibodies may fade fast raising questions about vaccines.

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And then but you can find answers sort of both ways. So many have deemed the question impossible to address. This epidemic is so recent. There have been few well-monitored re-infections. So here on the left you see one saying my patient caught COVID-19 twice, so long to herd immunity, you know. Is there no immunity that you get from this disease? And then another article simultaneously or very nearly simultaneously can you get COVID again? It's very unlikely, experts say.

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So, it would be really great to answer this question and I'm here to say we can answer this question. On the contrary, there's not nothing known but we do know something about the durability of immunity to SARS-CoV-2 and the reason we know it is because of the historical contingencies of evolutionary biology. SARS-CoV-2 is a coronavirus like multiple other coronaviruses that are listed here SARS-CoV-1 the three- the human coronaviruses you may be familiar with that are- cause the common cold regularly, MERS [Middle East Respiratory Syndrome] is another example, and those coronaviruses all have genetic differences that tell us how closely related they are to each other. So, we can learn something from the other coronaviruses about SARS-CoV-2, and there's a very rigorous way of doing that, and that is by phylogenetic analysis.

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So, if we look at the different viruses, we can see how closely related they are, and the fact is that viruses can't evolve super quickly. They have limits, the rate at which they can evolve and how fast they can change, and we have methods in evolutionary biology to understand how fast they change across a phylogenetic tree such as this one which we reconstructed from the genome sequences.

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So, the kind of data that we want to take into account to do this is to look at continuous issue- we want to do continuous ancestral and descendant state inference under a Brownian-motion model of trade evolution and the kind of data we're looking at is this Anti-N which is one of the genes of the coronavirus IgG which is just an antibody type across time. So, this paper by Edridge et al. very fortunately looked at the three- I'm going to talk about three of the seasonal coronaviruses here, over time, and examined when they had peaks: these starry points which indicate that there was an infection in an individual. These are in the seasonal coronaviruses, and then that allows us both to understand what levels of antibody allow an individual to get infected but also how long it takes for them to decline between times of being infected.

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So, analyzing both of those things across the coronaviruses, and I'm sorry this appears much more pixelated on the screen than it did when I made it, but we're able to actually characterize the peak normalized antibody levels over time based on that kind of data for these human coronaviruses. We're also able to characterize the daily probability of infection or how long over time it takes- how likely are you be infected as your antibody level declines. This is for these seasonal coronaviruses for which that longitudinal data over many many years, that was over decades, was collected. Now in addition to understanding this about the seasonal coronaviruses, they're embedded in this phylogenetic tree that it allows us- enables us to also study the seasonal coronaviruses for which we don't have daily probability of infection data, but for which we do have some data on the IgG, IgA, IgM on this information about the antibody level.

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So combining that data based on what we already know about SARS-CoV-2, SARS-CoV-1, MERS-CoV, and these three seasonal coronaviruses, combined with the information on daily probability of infection, we're able to use phylogenetic methods to impute what the daily probability is an infection and what the rest of the antibody decline is probably like for each of these zoonotic coronaviruses enabling us to estimate the time of waning immunity, the problem of infection over time, and the probability density of re-infection.

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So, what this gives us is this probability of density of reinfection over time. This is an axis of days on the axis here, and you can see that although there's some differences between the antibody decline and the daily probabilities of infection among these different diseases, the overall distribution of when you get in of a time of reinfection does not appear to be all that different between these different diseases.

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Consequently, what we can conclude in our main analysis is the following: That the median time to reinfection by SARS-CoV-2 appears to be about 1 year, 7 months. SARS-CoV-1 is quite longer. SARS-CoV-2 by our best estimate SARS-CoV-2 again 1 year, 7 months. MERS 1 year, 4 months although it's never been, you know, you don't get reinfections because the zoonotic disease does not spread from human to human. And for the different seasonal coronaviruses, we get somewhere between four to six years for the duration of that.

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So, what are my conclusions? They are that this ancestral and descendant states estimate of the timing of the waning of immunity can facilitate a quantitative analysis of all policy decision making with regard to individuals who've recovered from COVID-19 and who may be viewed as immune to reinfection but may not be after some time. Secondly, the durability of immunity has implications for the deployment of recovered health care workers, of travel restrictions, decisions on how students retain their education, prospective vaccination protocols for clinical trials as well as the opening and closing of economic sectors in response to predictive models of the epidemic. Our estimate argues strongly against the claim that a long-standing resolution of the epidemic could arise due to any kind of herd immunity from natural infection. Such a strategy jeopardizes millions of lives, entailing high rates of infection morbidity and death every 1.5 years. It provides some guidance as to the likely time scale of immunity conferred by a typical vaccine. I'll have a caveat about that in a moment. This approach has general applicability to rapid prediction of parameters for any novel pathogens, provided they're embedded in a plate containing three or more previously studied human pathogens.

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I just want to give you a few caveats to make sure it's clear what we can and can't say from this. The research addressed durability of immunity in response to typical natural infections under endemic conditions. The durability in response to vaccination requires a little further analysis because vaccination doesn't give you the same antibody level response that natural infection does, necessarily. And also, we're under pandemic conditions until the world's population has sort of been exposed to the disease or vaccination and so that means that some of the timings are going to be slightly different for some complicated epidemiological reasons. Our estimate and some certainty should be understood as a prediction of the average durability not universal to everybody. We know that different antibody levels are sparked by different infection levels and by different vaccines so each individual is slightly different this is what's typical. And because SARS-CoV-2 is a novel virus the human immune system, the reinfection may not exhibit the same severity as first infections. We will have to see as time goes on. Thanks very much for the time and from the support from NSF to do this very interesting research.